

# SECTION OF BIOLOGICAL AND MEDICAL SCIENCES

## MISCARRIAGE: MARKING TIME

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### Abstract

Preterm labor (PL) was, is and will be the most important problem of modern obstetrics, because the overwhelming majority of perinatal losses are determined by the prematurity of newborns.

According to the exact definition of the world-famous specialist G. C. Di Renzo at COGI World Congress: preterm labor (PL): the reasons are unclear, the diagnosis is difficult, the methods are debatable, the results are unpredictable, the price is huge.

We have conducted a pilot study of the combined use of vaginal progesterone and obstetrical pessary. The obtained results are encouraging and allow us to recommend the described above approaches for wide medical use. The proposed medical technology is approved by the Ministry of Health of the Republic of Belarus as an instruction for use.

**Keywords:** premature labour, short cervix, obstetrical pessary.

Preterm labor (PL) was, is and will be the most important problem of modern obstetrics, because the overwhelming majority of perinatal losses are determined by the prematurity of newborns. The sad truth is invariable: **no one can successfully nurse to health children with critically low body weight!** And that is understandable. Physiology says that the viability of a newborn is determined by gestation period of 28 weeks or more, weight 1000 g or more, and height of 35 cm or more.

According to the exact definition of the world-famous specialist G. C. Di Renzo at COGI World Congress: preterm labor (PL): the reasons are unclear, the diagnosis is difficult, the methods are debatable, the results are unpredictable, the price is huge.

Premature infants account for 60–70% of early neonatal and children’s mortality. If premature babies survive they often have severe complications up to disability.

The development of new effective approaches to the prevention and treatment of miscarriage is the “top priority” in modern clinical obstetrics. In this regard each week of intrauterine fetal development during preserved pregnancy is important. It is enough just to look at several figures: perinatal mortality (PM) in case of delivery at term varies widely with good prognosis values 2–4 %, in case of preterm labor PL – 10 %, and in case of preterm labor PL in gestation periods of 22–24 weeks – 70 %.

The incidence of PL has remained constant for 25 years: the PL rate fluctuates around 10% of the total

number of births (WHO, 2018). Moreover, the statistical calculations of this organization are not optimistic: at present 5 million premature labors per year are registered in the world, and their number is increasing. As a result 1.1 million premature babies die from complications associated with preterm labor (Fact sheet Reviewed November 2016).

Finally, the economic consequences: the additional costs of solving the health problems of children under 18 years of age who were born prematurely in comparison with children born at term:

- 34-36 weeks - \$ 35,471
- 31-33 weeks - \$ 95,760
- 28-30 weeks - \$ 146,847.

Specialists are not fine with such results. Therefore, it is clear that preterm labor (PL) is perhaps the most popular topic in the rhetoric of obstetricians-gynecologists. Quite often, the question formulation is of the following nature: **miscarriage and irreducible frequency of preterm labor, is this problem unsolvable or unsolved?**

At the same time despite the huge amount of research devoted to PL, in our opinion, there are many misconceptions that do not allow to move forward effectively.

**Firstly**, this is due to the “trap of knowledge”, the prevailing stereotypes of thinking and refusal to accept the complexity of the problem. Preterm labor (explicitly or implicitly) is usually considered as one disease. Considering preterm labor as a single condition that can be predicted with a single analysis and provided with

preventive care with a single intervention is an incorrect concept.

An important step forward would be the rethinking of this problem so that it would become solvable.

One of the main obstacles to understanding this problem and finding effective tools to solve it is that premature labor (explicitly or implicitly) is considered as one disease. Although it is well known that two-thirds of preterm labors occur after the spontaneous onset of labor activity, and the rest are preterm labors according to the indications, but the causes of spontaneous preterm labor and preterm labor according to the indications are different. Spontaneous preterm labor is a syndrome caused by many reasons, one of them is a decrease in the action of progesterone which induces cervical ripening. Shortening of cervix uteri <25 mm according to echography (detected in the II trimester) is an important prognostic factor of spontaneous preterm labor. [1,16].

The prospects for the problem of preterm labor in most countries (especially in those where there are problems with low birth rates) are not encouraging: there is an obvious increase in the incidence of PL. This trend is inevitable for a number of reasons: due to an increase in the proportion of older pregnant women (35+), high frequency of extragenital diseases, intrauterine hypoxic states, and an increase in the number of pregnancies that have occurred using ART (assisted reproductive technologies, in particular IVF). The frequency of PL "according to indications" will objectively increase, since we are talking about the condition of fetus and newborn.

Therefore, today the efforts of specialists all over the world working in the field of prevention and treatment of spontaneous PL are aimed at solving at least two problems: development of new technologies for nursing the babies with critically low birth weight (500 - 1000 g) and prolongation of pregnancy till "acceptable" gestational age. If neonatology and pediatric intensive care are more relevant to solving the first problem, then the second problem is directly solved by obstetricians.

**Secondly**, we are talking about our idolatry for statistical indicators that are reasonably not reviewed for decades taking into account the new time and conditions in which we live. In our opinion, the titanic efforts to prolong pregnancy to 37 weeks are simply absurd and do not give anything except for the indicator of incidence of PL in registers and reports. All obstetricians-gynecologists know this! Every neonatologist will say that after 34 weeks (many believe that after 32 weeks) prematurity is not an unsolvable problem for a newborn. Everything is already fine with the maturity of surfactant at this term, and there is no point in conducting the prevention of respiratory distress syndrome RDS. In case of threat of PL the chronic intrauterine hypoxia of the fetus always persists to a greater or lesser extent. In the end this therapy for a month is a rather expensive procedure. Therefore, 34 weeks of pregnancy can be considered "acceptable terms".

In this work, the main focus will be on predicting spontaneous preterm labor based on the length of cervix uteri in the second trimester and its prevention by

means of mechanical correction, namely the use of obstetrical pessaries.

Isthmic-cervical insufficiency (previously called "cervical incompetence") can lead to late spontaneous abortion or early preterm labor within a few days or weeks after establishing diagnosis [1,12,13,15]. An isolated shortening of cervix in the second trimester of pregnancy is an example of asynchronous activation of the common path of the birth act, since patients do not have increased contractility of the uterus or signs of rupture of the membranes.

With the introduction of ultrasound diagnostic method, especially of transvaginal technique, into wide clinical practice the frequency of detection of this pathology has changed.

Ultrasound studies of cervix uteri began in the 1980s. [12,15,30,31,32,37]. In 1990, Andersen et al. published an observation in which 113 patients were examined by means of vaginal examination of cervix uteri, and the length of cervix uteri was determined using transabdominal and transvaginal sonography.

One way or another, the fact that the **risk of preterm labor depends on the length of cervix uteri, the timing of the shortened condition appearance (the sooner "short cervix" develops, the earlier preterm labor happens)**, has been known for quite a long time.

According to our data the frequency of detection of "short cervix" in the total population of pregnant women in the Republic of Belarus is about 25% [9,10].

These figures are quite comparable with statistics on the detection in our region of the incidence of isthmic-cervical insufficiency (ICI) after 18 weeks of pregnancy. Prospective studies of these patients show that they constitute the majority (more than 80%) of pregnant women who lose their pregnancy in the period of 12–20 weeks, have clinical picture of miscarriage, a progressive picture of "short cervix" and ICI.

The fact that "short cervix" is a real predictor of ICI and preterm labor suggests that the shortening of cervix uteri (as a sign of its functional insufficiency), along with other local signs (effacement, opening of cervical canal), is a reflection of the dynamics of subclinical asymptomatic (latent) beginning of the "first period of preterm labor" without active contractile activity of uterus. According to our data, 14% of pregnant women reach the term of 18 weeks with a shortened cervix and about the same number "do not reach" due to pregnancy loss for various reasons.

The interest in this issue is logical, almost everywhere there are technical capabilities for examination (ultrasound) which led to vigorous activity in a good sense of people who are not indifferent and curious regarding the question - "So what is "short cervix", and is it somehow related to the outcome of pregnancy and the problem of its premature termination?"

The analysis of the most significant and evidence-based studies as well as our own results allow us to draw some in our opinion important conclusions.

**Short cervix** (sonographically normal cervix is 35-48 mm) can serve as a prognostic sign of the risk of cervical insufficiency during pregnancy and the risk of

miscarriage. Thus, the sonographic criteria for detecting "short cervix" syndrome are the parameters: (= or <25 mm).

Probably, short cervix at small gestational age should be regarded as untimely "ripening" of cervix uteri and a pregnant woman entering the stage of "readiness for labor". Further, with an increase of gestational age, the intrauterine volume and intrauterine pressure increase. An increased load on cervix uteri will be especially marked, naturally, in case of multiple pregnancy, polyhydramnios, large fetus, etc. [11,12,14,15].

Further, the mechanisms similar to those at the beginning of the first period of labor are likely to be activated: an increase in the uterine tonus, the appearance of contractions and the development of premature labor.

**ICI** - painless dilatation of cervix uteri in the absence of uterine contractions (inability of cervix to remain closed during pregnancy). The clinical situation in which cervix uteri can be open all over or in the area of the internal orifice with a preserved length or shortened cervix.

**SC** - painless shortening of cervix uteri with the cervical canal closed all along and unchanged internal orifice.

Cervix uteri undergoes a physiological contraction, which begins at 28-30 weeks of gestation. Thus, the measurements of cervix which appear to be moderately short between 28 and 32 weeks and later have limited clinical value, and the physician should include gestational age into the assessment of the risk of prematurity.

The analysis of "risk factors" and possible causes of the development of "short cervix" shows their undoubted similarity with those in case of clinically manifested isthmic-cervical insufficiency, which confirms the assumption made above. And if one would refer to this condition as an early stage of ICI, it would become clear that its early diagnostics and correction are a promising direction for prevention and treatment of both ICI and preterm labor in general.

#### **Diagnostics of short cervix syndrome**

There is another "weak link" in the topic under discussion. The standard procedure for identifying ICI and monitoring of cervix uteri according to prevailing standards of thinking and various methodological approaches is addressed to 18 weeks of pregnancy and later. Then follows the diagnosis of ICI and certain prevention and therapeutic actions.

The development of this topic for us began in 2010-2011, when we happened to work as one of the centers in an international multicenter randomized study to research the effectiveness of vaginal progesterone use for the prevention of premature labor with a short cervix (<15 mm) after 22 weeks of pregnancy. This study is today known as the "study of R. Romero" [40].

During the study, the main question arose - **what should one do with a short cervix before this gestational age?**

In this regard, we organized and conducted a study that allowed us to assess the feasibility of diagnostic

and therapeutic activity in this category of pregnant women.

The study program involves two stages:

#### **■ I stage:**

Screening for the syndrome of "shortened cervix" in women at high risk of PL in the period of 11 - 12 weeks, re-examination of the high-risk group in the period of 18 - 21 weeks.

The method is accessible and easy to use. This work does not greatly burden the doctor, since it can be performed during the I-II trimester of pregnancy as an addition to screening for abnormalities of fetus (Down's syndrome) and re-examination of the high-risk group in the period of 18-21 weeks as an addition to screening (congenital defects, cardiac defects).

***The measurement of length of cervix uteri should be a part of standard sonographic procedure during I and II fetal screening to assess the risk of spontaneous termination of pregnancy/preterm labor in the future and should be recorded in the protocol!***

This allows predicting late abortions and early preterm labor at the early stages with clinically asymptomatic pregnancy complications.

To obtain adequate and what is important, reproducible information, the measurement of length of cervix uteri requires the compliance with a number of conditions and rules. This is especially important for the reason that it is possible that in the same pregnant woman the length of cervix will be measured by different specialists, which means that in the absence of standard the data in the dynamics will be incomparable.

#### **Correction of "short cervix" syndrome as method of prevention of late abortion and premature labor**

The high frequency of detection of syndrome of "short cervix" of uterus, the risk of developing ICI and premature labor against the background of this condition made it necessary to search for methods of correcting these conditions, especially in gestational periods of 12-20 weeks. We have to state that these terms can be **"considered the terms of not only diagnostic but also of therapeutic failure"** regarding the prevention of PL. What we really have in our practice: pessaries and cerclage - from 16 weeks of gestation, tocolysis (mimetics) after 22-24 weeks.

The shortening of length of cervix should lead to preventive measures.

In this regard, we used vaginal micronized progesterone preparations [9,17,21,24,23,28,29,40,41] in case of diagnosing "short cervix" syndrome at the second stage before using mechanical means.

#### **■ II stage:**

***Hormonal support with progesterone preparations at the early gestational age from the moment of short cervix detection (<25 mm)***

+

***The use of obstetrical pessary or suturing (after 14-16 weeks) in case of appearance of ICI or "-" dynamics***

The pessary or obstetrical suture is applied in case of indications: if there are clinical signs of ICI, one of which is a progressive shortening of cervix.

Vaginal micronized progesterone preparations are prescribed from the moment of short cervix detection until the pessary is inserted.

**If there is no clinical need, progesterone can be discontinued after the obstetric pessary is inserted. This is important because it reduces the drug load on the pregnant woman's body (!).**

In case of high risk of preterm labor in combination with short cervix, hormonal preparations administration should be continued until 34-36 weeks of pregnancy:

- *Obstetric history (premature labor occurred).*
- *Multiple pregnancy.*
- *Cervix conization.*
- *Muller anomaly and other abnormalities of uterus and cervix.*
- *Pregnancy after IVF.*
- *Infertility associated with luteal deficiency.*
- *Laboratory proven progesterone deficiency.*

**The role of progesterone, micro-elements and connective tissue in the development of ICI.**

The deficiency of progesterone leads to the reorganization of the components of connective tissue of cervix uteri which facilitates the processes of its shortening in women with undifferentiated connective tissue dysplasia (UCTD), at the same time, these processes are accompanied by a decrease of  $Mg^{2+}$  level in blood. In turn, under conditions of reduced  $Mg^{2+}$  concentration, the ability of fibroblasts to produce collagen is impaired, pathological activation of Ca-dependent contractile reactions in myometrium occurs, and the severity of threatening miscarriage (TM) increases [3,6].

The most significant for the processes of regulation of state of connective tissue (CT) is  $Mg^{2+}$  and  $Ca^{2+}$ , as well as their ratio in the body. So,  $Mg^{2+}$  is responsible for the structure of connective tissue (collagen, elastin, collagen fibers). In case of  $Mg^{2+}$  deficiency, the synthesis of structural components is slowed down, the processes of degradation of collagen fibers are strengthened, the ratio of collagen/elastic fibers is impaired towards an increase in the latter, the synthesis of defective collagen happens due to the disturbance of the structure and assembly of collagen fibers. In turn,  $Ca^{2+}$  determines the flexibility of elastin fibers and regulates the activation processes of elastase centers. The balance between  $Ca^{2+}$  and  $Mg^{2+}$ : in case of deficiency of  $Mg^{2+}$  and normal/elevated level of  $Ca^{2+}$ , the activity of proteolytic enzymes - metalloproteinases which cause degradation of collagen fibers, increases, that leads to excessive degradation of CT. The combination of progesterone and magnesium deficiency in the body of pregnant women of risk groups regarding the development of ICI can lead to the activation of degradation processes of connective tissue in cervix uteri, especially in the area of the internal orifice, which can become a trigger in the development of this pathology. Therefore, supplementation of ICI therapy with long-term *magnesium support* along with micronized progesterone can be considered expedient [7,8].

**The use of obstetrical pessaries for the prevention of miscarriage**

(in case of short cervix syndrome and ICI)

It is important to note that at the XI World Perinatal Medicine Congress "Global Changes in Maternal and Child Health Care" held in Moscow in June 2013 the position of scientists and practitioners regarding their attitudes to PL as well as the possibility of use and good effects from using obstetrical pessary have found confirmation in the reports of the leading experts in the world (Romero, Di Renzo, Fonseca, etc.) [4,5,9,19,20,21,42,43]. Di Renzo during his speech at the perinatal congress commented this as "equal effectiveness of three therapeutic approaches - the application of obstetrical pessary, suturing and vaginal progesterone. In this regard, vaginal progesterone and obstetrical pessary can be a safer alternative to suturing, since pessaries and progesterone are conservative, non-surgical interventions." At the same congress professor Fuchs (USA) reported an increase in the effectiveness of prolongation of pregnancy in case of combination of these two methods based on his experience of observations.

The trend towards using non-invasive methods of correction of ICI was observed for quite a long time and consistently. Although the discussions on this topic continue, the opinions voiced by well-known experts from various countries and scientific schools, as it is indicated above, at XI World Perinatal Medicine Congress "Global Changes in the Care of Mother and Child Health", are unanimously in favor of using obstetrical pessaries.

This is evidenced by a number of studies that are devoted in the world to the possibilities of using pessaries in real obstetrical practice.

In 28 clinical centers of the world, the studies of various designs of cervical pessaries are conducted [5,7,10]

- Great Britain, Spain, France, New Zealand, Republic of Belarus <http://clinicaltrials.gov> [9].

- Germany, <http://www.dr-arabin.de>

- Poland, <http://www.herbich.pl>

There are several hypotheses on how a pessary can prevent spontaneous preterm labor and Preterm Premature Rupture of Membranes (PPROM). Placing a pessary leads to a sharper angle between the body of the uterus and the cervix, and it lasts as long as the pessary remains in place. This change can prevent direct pressure on the membranes at the level of the internal orifice of cervix and on the cervix itself. As a result, the pressure of the uterine mass is more directed towards the lower anterior segment of the uterus.

The second hypothesis says that the pessary can prevent further opening of the internal orifice, against the background of which the stratification of the amnion and chorion often occurs, in particular, when the pregnant woman is in an upright position. The fetal membranes are sensitive to mechanical damage and other pathological effects (infection and inflammation).

And finally, the third option suggests that the pessary protects the cervical mucous plug. This can be achieved by pessary fixation of the remaining tissue of cervix. A number of works prove that it is the mucous plug that plays an important role in maintaining pregnancy by protecting the uterine cavity from an ascending infection, and its rarefaction induces labor [28,46].

There are two types of structures: obstetrical unloading pessary (which reduces the load on the cervix) and cervical (which has a direct effect on cervix, mechanically preventing its shortening and smoothing) that are most common in the obstetrical world practice of recent years.

#### **Differentiated approach to the use of obstetrical pessaries**

The existing treatment methods for ICI are usually aimed at mechanical enhancing of the locking function of the internal orifice of cervix and are used against the background of a pronounced clinical picture (opening of external and internal orifice, shortening of cervix, clinical manifestations of threat of pregnancy termination, etc.). Already known invasive methods of treatment of ICI (applying a circular suture to the cervix in various modifications) [25] require careful preparation, hospitalization of a woman to obstetrical-gynecological hospital, the

use of anesthesia, are a psychologically traumatic factor for a pregnant woman, that, in turn, can aggravate the course of threatening abortion on the background of ICI.

The method of using obstetrical unloading pessary, which has been widely recognized in recent years, is non-invasive, does not require special training and participation of related specialists (anesthesiologist), causes less psychological trauma to a pregnant woman. One of the main advantages of this method is the possibility of its successful use at the stage of preclinical manifestations of ICI (according to ultrasound, medical history, presence of the above risk factors) and its preventive effect [2,9,10], as well as the possibility of its use on an outpatient basis.

#### **Obstetrical Unloading Pessary** (plastic and silicone)

In 1993 an obstetrical unloading pessary was developed (Figure 1).



*Figure 1. Obstetrical plastic unloading pessary*

In our opinion, the total impact of pessary is based on the “closing” of cervix, redistribution of gestational sac pressure, sacralization of cervix and provides a decrease in the tendency to form a shortened and partially open cervix.

Thus, the obstetrical unloading pessary may be the choice in those clinical situations where the risks of miscarriage are determined by a large intrauterine volume or pressure. In this regard, there is a force pressure on the lower segment and cervix. In these situations, it is the unloading mechanism that can be considered appropriate for use.

The indications for use of the obstetrical unloading pessary are: the presence of functional or organic isthmic-cervical insufficiency during pregnancy (short cervix syndrome after 16 weeks):

- Polyhydramnios
- Large fetus
- Multiple pregnancy
- Low location of the presenting part of the fetus

- Prolapsing fetal bladder
- Critically short cervix - less than 1.5 cm

In recent years, a similar silicone product has been used in practice. This pessary has the same dimensions, the same shape, only different material: silicone. The need to develop and use such a pessary is due to the fact that a number of patients whom this pessary was inserted complained of tightness and pain during the insertion and treatment. Others psychologically did not accept this model, and now, if there are alternative options, they agree to use the method. In case of threatening PL, this is an essential part of success: patient peace and comfort when using the method.

***Therefore, the plastic pessary over time is likely to go down in history and give way to a new more convenient and promising product.***

On a scheduled basis the pessary is removed at the gestational age of 37–38 weeks.

#### **Silicone pessary: cervical perforated**

In a number of clinical situations, an alternative to suturing is the insertion of cervical pessary (Figure 2).



Figure 2. Silicone cervical perforated pessary

The mechanism of action of such a pessary consists in closing cervix uteri by the walls of central opening of pessary, due to physiological sacralization of cervix and partial transfer of intrauterine pressure to the anterior wall of the uterus. [5,6,26].

The perforated model provides a good fluid outflow in case of increased vaginal secretion and is more preferable in pregnant women [1,39].

Indications for use of this type of pessary:

- ICI of functional and organic origin, including for the prevention of circular suture failure during surgical correction of ICI;
- pregnant women from risk groups for miscarriage;
- patients with a history of miscarriages in late gestational age, PL, suffering from habitual miscarriage;
- pregnancy after a long period of infertility;
- patients with dysfunction of the ovaries, genital infantilism;
- patients with the threat of miscarriage of the present pregnancy, in combination with progressive changes of cervix;
- patients with multiple pregnancy, including those after assisted reproductive technologies;
- patients with a threat of miscarriage of the present pregnancy and altered psycho-adaptation reactions in relation to the termination of pregnancy.

The main method of control of the correct insertion and position of this type of pessary is ultrasonographic imaging of cervix of a woman using pessary.

In foreign studies (level of evidence B), the effectiveness of obstetrical pessaries in women with a short cervix was studied. It was demonstrated that in pregnant women with cervix length 25 mm or less to whom a pessary was inserted and expectant management was used, preterm labor was only in 6% versus 27% among the women of control group who did not use pessaries (odds ratio 0,18; 95% CI 0.08-0.37;  $p < 0.0001$ ). Patients with cervical lengths less than 25 mm, according to transvaginal ultrasound imaging, have an extremely high risk of PL and need preserving therapy.

The study of the possibility of use and effectiveness was carried out in a prospective, open multicenter,

randomized study (level of evidence B): Cervical pessary in pregnant women in the prevention of preterm labor (Maria Goya, Laia Pratcorona, Carme Merced, Carlota Rody, Leonor Valle, Azahar Romero, Miquel Juan, Alberto Rodriguez, Begoca Mucoz, Belin Santacruz, Juan Carlos Bello-Mucoz, Elisa Llorba, Teresa Higuera, Luis Cabero, Elena Carreras, on behalf of the Pesarío Cervical para Evitar Prematuridad (PECEP) Trial Group). [26,31,32,37,44,45].

The dynamics of research results and clinical recommendations in the world on the use of pessaries looks interesting. If at the beginning of the way it was a statement that it is better to be with pessary than without it.

The recent years are characterized by the breakthrough of a large number of studies in which the clinical effectiveness of pessaries has been proven: in case of short cervix and multiple pregnancy, it reduces the incidence of PL [27]; in case of multiple pregnancy the use of vaginal progesterone with the use of pessary [25]; in case of multiple pregnancy and short cervix the use of a pessary reduces the incidence of PL up to 34 weeks of gestation [1].

The results of the analysis of peculiarities of the course of pregnancy of women using pessaries allow us to draw the following conclusions:

Singleton pregnancy and short cervix:

1. The need of ultrasound screening for all women with a singleton pregnancy is being discussed. Doubts are raised mainly regarding the quality guarantee, as well as the risk of unnecessary interventions in case of singleton pregnancy in the absence of symptoms of PL or PL in history. However, in those countries where the studies of the collar space are conducted (I screening – 12 weeks), this should be carried out under the condition that medical workers are trained, and the results obtained must undergo an external quality assessment [2,11,30,33,37,44].

2. The use of pessaries reduced the frequency of adverse outcomes and ensured the prolongation of pregnancy in women with a short cervix (<25 mm) between 18 and 22 weeks [27]. In the group of pregnant women using pessary, there were fewer births before 34 weeks of pregnancy (6% versus 27%), fewer births be-

fore 37 weeks of pregnancy (22% versus 59%) and before 28 weeks of pregnancy 2% versus 8%). The use of pessaries in the II trimester in case of cervical length (<25 mm) in another study at the time of labor with pessaries 37.8 versus 28.3 weeks [32,46].

Twin pregnancy:

2. In pilot projects of “case – control” type when pessaries were used in case of short cervix, it was noted that pessaries can significantly reduce the frequency of PL. The average gestational age was 35+6 weeks with pessaries versus 33+2 weeks. In another study in case of cervix (<25 mm), the term of labor occurred 4 weeks later than in the control group. However, such studies are extremely important, given the high incidence of PL in case of multiple pregnancy [25].

Pregnancy in patients after radical conization of cervix uteri:

3. A specific group of patients. They usually seek medical advice early. Of course, there is a connection between surgery, trauma and the risk of PL. Cerclage does not quite fit and has no effect. Therefore, the obstetrical pessary, especially in combination with vaginal progesterone may be the method of choice [35,36,38].

The possibility of using additional medications:

4. When using pessaries there are no contraindications to the use of medications such as vaginal progesterone, indomethacin, antibiotics. If a further shortening of cervix is observed against the background of the pessary, the prescription of vaginal progesterone should be considered. In the early stages (starting from 12 weeks), they start with vaginal progesterone, and then pessary is inserted or both methods are prescribed simultaneously in patients with cervical length <15 or 20 mm [10,32,46].

It should be noted that both types of pessaries are not alternative technologies. A differentiated approach to the use of various types of pessaries based on the indications (see above) should be considered as correct. The obstetrical unloading pessary is most effective in those cases where the possibilities for efficient use of cervical pessary are limited, and vice versa.

The obtained convincing data on the good clinical effect when using obstetrical unloading pessary in the Republic of Belarus led to the fact that they not only entered into the National Protocol in section “Miscarriage”, but also led to the fact that surgical cerclage is used very rarely (usually in cases when there are contraindications to the use of obstetrical pessary).

The advantages of using pessaries in obstetrics can be determined as follows:

- use of method on an outpatient basis;
- absence of necessity for hospitalization and anaesthetic support;
- painlessness and ease of pessary insertion;
- reducing the risk of infection and injury during labor;
- economic expediency.

Despite the encouraging results of using various types of obstetrical pessaries in case of threat of preterm labor, it must be remembered that timely prevention of

ICI is a much more effective tool, since it is implemented until the threat of termination of pregnancy appears as such.

The main principles of ICI prevention are:

- restoration of integrity of cervix uteri in case of its traumatization immediately after childbirth, abortion, diagnostic curettage;
- correction of discovered ICI at the stage of pregravid preparation (excision and suturing of old lacerations, use of dermal fillers based on hyaluronic acid which effectively compensates for the lost volume and increases hydrophilicity of tissues;
- prevention of sexually transmitted infections;
- support of optimal pH of genital tract;
- timely identification of risk factors for the development of ICI and minimization of their influence;
- progesterone support of pregnancy against the background of ICI [9,10,14, 14,24,34,36].

Thus, in conclusion, we would like to draw attention to another important circumstance. Obstetrical pessaries can be effectively combined with other methods of preventing PL such as vaginal progesterone. This is extremely important at later gestational age, when intrauterine volume and pressure increase and additional support for pregnancy is required. This is especially true when a clinically significant ICI starts to develop after 16 weeks of pregnancy. It is also interesting that there has appeared evidence for the effective use of vaginal progesterone in combination with obstetrical pessary for twin pregnancy [25,27,33].

We have conducted a pilot study of the combined use of vaginal progesterone and obstetrical pessary. The obtained results are encouraging and allow us to recommend the described above approaches for wide medical use. The proposed medical technology is approved by the Ministry of Health of the Republic of Belarus as an instruction for use “Differentiated use of various types of obstetrical pessaries in case of short cervix syndrome and isthmic-cervical insufficiency for the prevention of preterm labor”.

The results of studies in the Republic of Belarus on treatment and prevention of preterm labor:

■ ***The increase in the number of pregnancies that ended in childbirth at term of 32 - 37 weeks due to prolongation of term of 22-27 weeks - 20%***

■ ***Decrease in the number of clinical ICI: about 10%***

■ ***Reducing complications associated with fetoplacental insufficiency and intrauterine hypoxia.***

■ ***The questionnaire demonstrates a higher level of psychological comfort in pregnant women (confidence and security after pessary insertion) in case of threat of termination of pregnancy.***

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